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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,760	03/31/2004	Joel E. Bernstein	41959-102739	5267

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BARNES & THORNBURG LLP
P.O. BOX 2786
CHICAGO, IL 60690-2786

EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

NOTIFICATION DATE	DELIVERY MODE
02/28/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patent-ch@btlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/813,760	BERNSTEIN, JOEL E.	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9, 11-23 and 25-37* is/are pending in the application.

4a) Of the above claim(s) *16-23 and 25-37* is/are withdrawn from consideration.

5)☐ Claim(s) *13-15* is/are allowed.

6)☒ Claim(s) *1-9 and 11-12* is/are rejected.

7)☐ Claim(s) _ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114.

2. Acknowledgement is made of applicant's filing of an amendment on 11/26/07. By the amendment, claims 1, 5, 7, 11 and 13 have been amended and claim 24 has been cancelled. Claims 1-3, 5-9 and 11-15 are currently pending for prosecution on the merits.

3. Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Objections

4. Claims 5 and 11 are objected to because of the following informalities: Improper Markush-type language "selected from the group consisting...or..." is used. Suggest rewording of "selected from the group consisting of...or..." to "selected from the group consisting of…and…".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-9 and 11-12 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for the specific hepatotoxic compound such as acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium and valproic acid, does not reasonably provide enablement for "a hepatotoxic compound". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; the breadth of the claims; the amount of direction or guidance presented; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The present invention is drawn to a composition one or more of hepatotoxic compound, about 5mg to about 500 mg of methionine and about 10mg to about 500mg of nicotinamide.

The interpretation of the instant claims allows for the inclusion of any known hepatotoxic compound or drug that are known to exist and those that may be discovered in the future.

It is generally known today that "the diagnosis of hepatotoxicity remains a difficult task because of the lack of reliable markers for use in general clinical practice. To incriminate any given drug in an episode of liver dysfunction is a step-by step process that requires a high degree of suspicion, compatible chronology, awareness of the drug's hepatotoxic potential, the

exclusion of alternative causes of liver damage and the ability to detect the presence of subtle data that favors a toxic etiology…" (see World J Gastroenterol 2007, 21; 13(3):329-340); and that "it is difficult to identify a drug reaction with certainty…" (Lee, W.M., N. England J. Med., 349;5, 2003, pp. 474-485); "Predicting idiosyncratic hepatotoxic reactions has been a formidable challenge..." (Willett et al., Society of Toxicology, 2004, pp. 1-16).

The relative skill of the artisan and the unpredictability of the pharmaceutical art are very high. To practice the instant invention to the claimed scope, applicant would have to (i) screen numerous possible compounds characterized as "hepatotoxic compound, (ii) assay to find out which compounds are able to induce hepatotoxicity at what concentration level and then (iii) extrapolate the test and result to the claimed invention. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)), the skilled artisan would have not known how to extrapolate the examples provided in the instant specification ("acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium and valproic acid" are set forth as suitable working examples) to the larger and highly varied genera of compounds that are characterized by "hepatotoxic compound", without undue amount of experimentation.

As discussed above, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art, and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to make/use the claimed "hepatotoxic compound" that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 7, 8, 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim 1 recites transitional phrase "consisting essentially of" which limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. However, the dependent claim 7 introduces the additional component such as folic acid that is known to affect the basic and novel characteristics

of the composition. The specification discloses that the addition of folic acid to the composition further mitigates the hepatotoxic properties (para. [0007]).

As discussed above, it is clear that the instant term "consisting essentially of" allows for the inclusion of other ingredients or components that materially affect the basic and novel characteristics of the claimed composition, and thus is interpreted as fully open transitional phrase.

Response to Arguments

7. Applicant's arguments filed 11/26/07 have been fully considered but they are not persuasive.

In response to applicant's argument that the recitation of "used in treatment of human disease" in claim 1 remove any need for "undue experimentation" to determine a "hepatotoxic compound" when used in the treatment of human disease, the examiner recognizes that "the diagnosis of hepatotoxicity remains a difficult task because of the lack of reliable markers for use in general clinical practice. To incriminate any given drug in an episode of liver dysfunction is a step-by step process that requires a high degree of suspicion, compatible chronology, awareness of the drug's hepatotoxic potential, the exclusion of alternative causes of liver damage and the ability to detect the presence of subtle data that favors a toxic etiology…" (see World J Gastroenterol 2007, 21; 13(3):329-340); and that "it is difficult to identify a drug reaction with certainty…" (Lee, W.M., N. England J. Med., 349;5, 2003, pp. 474-485); "Predicting idiosyncratic hepatotoxic reactions has been a formidable challenge..." (Willett et al., Society of Toxicology, 2004, pp. 1-16). Thus, the skilled artisan would have not know how to extrapolate

the examples provided in the instant specification ("acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium and valproic acid" are set forth as suitable working examples) to the larger and highly varied genera of compounds that are characterized by "hepatotoxic compound", without undue amount of experimentation.

Allowable Subject Matter

8. The following is a statement of reasons for the indication of allowable subject matter: The most relevant prior art of record which the instant rejection is relied upon (Korger and/or Yang) fails to teach that "much lower dosages of nicotinamde and methionine, administered in a single dosage from with a hepatotoxic drug such as acetaminophen, given by different routes of administration than Kroger, would provide safe and effective hepatoprotection from hepatotoxic drug".

Conclusion

9. Claims 13-15 are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614